UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/672,069	09/25/2003	Tariq M. Rana	UMY-062	4721

959 7590 02/12/2007
LAHIVE & COCKFIELD, LLP
ONE POST OFFICE SQUARE
BOSTON, MA 02109-2127

EXAMINER	
CHONG, KIMBERLY	
ART UNIT	PAPER NUMBER
1635	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/12/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/672,069	RANA, TARIQ M.	
	Examiner	Art Unit	
	Kimberly Chong	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11/13/2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,4,33,39 and 84-90* is/are pending in the application.

4a) Of the above claim(s) *19,21,22,27,34-36,40-63 and 91-108* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,4,33,39 and 84-90* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *25 September 2003* is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2/27/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I, claims 1, 3-4, 33, 39, 84 and 86-90 in the reply filed on 13 November 2006 is acknowledged. The traversal is on the grounds that a search of the inventions Group I and Group IV would be coextensive. Applicant's arguments are persuasive and Group IV, claims 85-90, will be examined with Group I. Claims 19, 21-22, 27, 34-36, 40-63 and 91-108 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Therefore, the requirement with regard to Groups II, III and V-IX is still deemed proper and is therefore made **FINAL**.

Status of Application/Amendment/Claims

Applicant's response filed 13 November 2006 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 24 October 2006 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

With entry of the amendment filed on 7/11/2005, claims 1, 3-4, 33, 39 and 84-90 are under examination and claims 19, 21-22, 27, 34-36, 40-63 and 91-108 are

withdrawn from further consideration. Applicant has canceled claims 2, 5-18, 20, 23-26, 28-32, 37-38 and 64-83.

Response to applicant's arguments filed 04/24/2006 is obviated in view of the claim amendments and new grounds of rejection below.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 86 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 86 is drawn to a siRNA wherein the antisense strand is further modified upstream and downstream of "the cleavage site referencing the antisense strand". It is unclear what is the cleavage site of a siRNA and further it is unclear where the cleavage site in reference to the antisense strand is located.

Claim 86 recites the limitation "3 nucleotides downstream of *the cleavage site*" in lines 3 and 5 of the claim. Claims 1, 84 or 85, from which claim 86 depends, do not recite a cleavage site and therefore there is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 3-4, 33, 39 and 84-90 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tuschl et al. (WO 22/44321), Eckstein et al. (U.S. Patent No. 5,672,695) and Parrish et al. (cited on IDS filed 02/25/2006).

The instant claims are drawn to a small interfering RNA (siRNA) comprising a sense strand and an antisense strand wherein the antisense strand is complementary to the sense strand and has a sequence sufficiently complementary to a target mRNA, wherein the antisense strand is modified by the substitution of each uridine with 2'-fluoro uridine and each cytidine with a 2'-fluoro cytidine such that in vivo stability is enhanced as compared to a corresponding unmodified siRNA (claim 1) wherein the target mRNA specifies the amino acid sequence of a cellular protein or specifies the amino acid sequence of a viral protein (claims 3 and 4). The claims are further drawn to a siRNA wherein the siRNA is between 15 to 25 in length (claim 33) and a composition comprising said siRNA and a pharmaceutically acceptable carrier (claim 39). The claims are further drawn a siRNA wherein the sense strand is unmodified (claim 84), wherein the sense strand and antisense strand are modified by the substitution of each uridine with 2'-fluoro uridine and each cytidine with a 2'-fluoro cytidine (claim 85), wherein the antisense strand is further modified by the substitution of each adenosine with a 2'-deoxy adenosine and the substitution of each guanosine with a 2'-deoxy guanosine (claim 87). The claims are further drawn to a siRNA wherein the antisense

and sense strands are aligned such that the siRNA has 3' 2-nucleotide overhangs, wherein the overhangs are dTdT or UU (claims 88-90).

Tuschl et al. teach a siRNA, 19-25 nucleotides in length (see page 4, lines 1-4) wherein the siRNA comprise sugar or backbone modifications to increase *in vivo* stability and teach a preferred embodiment wherein the 2'-OH group is modified with a 2'-fluoro group, for example (see page 6, lines3-6). Tuschl et al. teach gene silencing from eukaryotic, plant cells or viral-infected cells (see page 8, lines 11-19). Tuschl et al. teach the 3' ends can be modified by substitution of the 2 uridine nucleotides with 2'-deoxythymidine or with UU nucleotides (see page 48, lines 1-18). Tuschl et al. further teach a composition comprising a siRNA as described above and a pharmaceutical carrier (see page 9, lines 11-15).

Tuschl et al. does not explicitly teach cytidine or uridine nucleotides in the antisense or sense strands having 2'-fluoro modifications nor specifically teach adenosine or guanosine nucleotides in the antisense or sense strands having 2' modifications. However, Tuschl et al. clearly recognize and teach that 2'-modifications enhance the nuclease stability of siRNA molecules. Tuschl et al. appear to recognize that chemical modification of the 2'-OH is a result-effective variable that may enhance nuclease resistance on the one hand and modulate siRNA activity on the other. Furthermore, Tuschl et al. suggests several types of substituents that may be used to replace the 2'-OH group, namely 2'-fluoro (see page 6, lines 1-4).

Likewise, Eckstein et al. recognizes that chemical modifications of the 2' position of a RNA is a result-effective variable and teach the 2' hydroxyl of a RNA molecule is

susceptible to degradation by nucleases and modification of 2' hydroxyl position of the ribose sugar enhances the stability of RNA molecules (see column 2, lines 55-60). Eckstein et al. teach preferred modifications of the cytidine and uridine with 2'-fluoro analogues (see column 4, lines 9-25).

Parrish et al. teach a double stranded RNA capable of interfering with gene expression and teach incorporation of different chemical modifiers at the 2' position enhance the molecules specificity and specifically teach modification of the cytidine and uridine nucleotides with a 2' fluoro group as well dsRNA with either the sense or antisense strands unmodified are capable of RNA interference (see Figures 5 and 6).

It would have been obvious to one of ordinary skill in the art at the time the invention, and a matter of routine experimentation, to use the general conditions taught by Tuschl et al. for making 2'-modified siRNA to discover the optimal number and placement of 2'-sugar modifications in any siRNA molecule, such that the resulting siRNA molecule was endowed with maximum stability and functionality. Additionally, it would have been obvious to one of ordinary skill in the art to incorporate known modifications, such as 2'-fluoro modifications of cytidine and uridine as taught by Eckstein et al. and Parrish et al., to impart increased stability and functionality in any siRNA because as stated by Eckstein et al., and well known to one of skill in the art that RNA has very low stability under physiological conditions and therefore modifications of RNA will provide therapeutic RNA with enhanced stability against chemical and enzymatic degradation.

One would have been motivated to create such compounds with increased stability and functionality, and since siRNAs are taught by Tuschl et al. as being useful in cell culture and in whole organisms for elucidating gene function in culture and in whole organisms (paragraphs 29-30), which may be considered to be nuclease-rich environments. One would therefore be motivated to chemically enhance the siRNA's resistance to nucleases while preserving or maximizing its activity in order to most effectively target the desired gene. Further, one would have been motivated to search for particular chemical modifications by routine experimentation of determining the optimum number and placement of the 2'-modifications to see how well the modifications were tolerated with respect to stability and functionality of the dsRNA. Eckstein et al. provide motivation to substitute the 2' positions of cytidine and uridine in siRNA molecules with 2'-fluoro groups to improve the efficacy because Eckstein et al. teach such modifications slowed down the degradation of the RNA by nucleases (see column 3, lines 36-59). Moreover, Parrish et al. provide motivation to search for particular chemical modifications by routine experimentation to determine the optimum number and placement of the 2'-modifications in either the sense or antisense strand of a dsRNA that would enhance the molecules stability.

One would have a reasonable expectation of success given that Tuschl et al. teach how to make and use virtually any siRNA to any gene provided the target sequence is known and Parrish et al. and Eckstein et al. teach known 2'-fluoro modifications increase RNA nuclease resistance. Further Tuschl et al. teach that

methods of RNA synthesis are known in the art, as evidenced by the examples provided therein.

Thus, the invention as a whole would have been prima facie obvious to one of skill in the art at the time the invention was made.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly Chong whose telephone number is 571-272-3111. The examiner can normally be reached Monday thru Friday between 7-4 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached at 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For more information about the PAIR system, see http://pair-direct.uspto.gov.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Kimberly Chong
Examiner
Art Unit 1635

SEAN McGARRY
PRIMARY EXAMINER
1635